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 TITLE: MACROCYCLIC CHELATES AND METHODS OF USE THEREOF.
 MACROCYCLISCHE CHELATE UND VERWENDUNGSVERFAHREN.
 MAKROCYCLISCHES CHELATES ET LEURS MODES D'UTILISATION.
 CHELATES MACROCYCLIQUES ET LEURS MODES D'UTILISATION.
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Chemical	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 110, no. 18, 31st August 1988, pages 6266-6267, American Society; C.F. MEARES et al.: "The peptide way to macrocyclic bifunctional chelating agents: synthesis of 2-(p-nitrobenzyl)-1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid and study of its yttrium (III) complex"	
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	tетраакетициклические бифункциональные хелатирующие агенты: синтез 2-(p-нитробензил)-1,4,7,10-тетраазациклододекан-N,N',N'',N'''-тетраакетициклические кислоты и изучение их комплексов с yttrium (III)	
	useful for binding metals other than copper, such as indium. These compounds are useful for imaging of tumors. The usefulness of radionuclide materials in cancer therapy is disclosed in the article, Kozak et al., "Radionuclide-conjugated monoclonal antibodies: A Synthesis of Immunology, in Organic Chemistry and. . . from the group consisting of hormones, steroids, enzymes, and proteins. These haptens are desirable because of their site	

specificity to **tumors** and/or various organs of the body. The preferred hapten for use in treating cellular disorders or various disease conditions is. . .

An embodiment of the invention involves a **ligand-hapten conjugate** of formula II: <image> wherein X and R._{sub1}. to R._{sub4}. are as previously defined in formula I. This conjugate chelates. . . conjugate. The kinetics of the formation reactions for these compounds are so rapid that it is desirable to have the **ligand-hapten conjugate** available in the pharmacy immediately prior to use. The conjugate can then be mixed in the radionuclide to form a. . . subsequently, the metal chelate conjugate formed can be purified by, for example, size exclusion high pressure liquid chromatography. A desirable **hapten** for the **ligand conjugate** can be selected from the group consisting of hormones, steroids, enzymes, and proteins.

The . . . Q can be a monoclonal antibody, wherein the antibody is directed and created against an epitope found specifically on the **tumor** cells. Thus, when Pb.²⁺.sup1..sup2. is transported to the antigen site and, subsequently, decays in secular equilibrium to Bi.²⁺.sup1..sup2. and its. . . be easily reached within the 1

hour

half-life of Bi.²⁺.sup1..sup2.. It is also possible to use this method to treat **cancers**, where the cells are widely differentiated. This might be preferred where only a long-range beta-emitter, such as Y.⁹⁰.sup0., is desired. . . . The . . . diagnostic tool. Thus, when Pb.²⁺.sup0..sup3. is linked by use of the chelate to a hapten, which specifically localizes in a **tumor**, then that particular localization can be three dimensionally mapped for diagnostic purposes in vivo by single photon emission tomography. Alternatively, . . .

The . . . to treat adult T-cell leukemia in mammals. T-cell leukemia is characterised by extraordinarily large amounts of IL-2 receptors on the **tumor** cells. The antibody localizes specifically to these **tumor** cells to deliver its radiation.

The . . . antibody B72.3, which binds specifically to a glycoprotein on LS-174T cells. This glycoprotein is also in humans who have colon **cancer**. The model system of this example is an athymic mouse, into which have been implanted LS-174T cells to develop a **tumor** on the flank of the animal where the cells were implanted. The diagnostic method used to visualize the growing **tumor** involves the following components. The chelate of compound 12 is first coupled

to

gadolinium or Pb.²⁺.sup0..sup3. by mixture of the. . . In . . . is injected or introduced into body fluids of a mammal. The gadolinium then localizes along with the antibody to the **tumor** and conventional resonance magnetic imaging techniques are used to visualize the **tumor**.

In . . . metal-labelled protein conjugate is similarly introduced into the mammal, but gamma camera or SPECT imaging is used to visualize the **tumor**.

CLMEN 13. A **ligand-hapten conjugate** of formula
II: <image> where R._{sub1}. to R._{sub4}., and n are as defined in claim
1;
and X' is as. . .